EDITORIAL

Contrasting Management of Small Cell Lung Cancer and Non–Small Cell Lung Cancer: Emerging Data for Low-Dose Computed Tomography Screening

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In 1973, Mary Matthews published a classic study describing the frequency of residual and metastatic tumor in patients undergoing curative resection of lung cancer.[1] The data set included 202 patients with all histologic types of lung cancer who had had their tumor resected for cure but died of all causes, including postoperative complications, within 30 days of surgery. At autopsy, residual cancer was observed in 35% of the patients. Of the 19 patients with small cell lung cancer (SCLC), however, 13 (70%) had residual disease (present at distant sites in 12 of 13). Although the number of patients was small, this paper changed how clinicians thought about SCLC. The initial sensitivity of SCLC to chemotherapy and radiotherapy was recognized by Watson and Berg.[2] Other clinical[3] and laboratory studies[4] established SCLC as a distinct clinicopathologic entity. Indeed, SCLC and non-SCLC (NSCLC) are generally discussed as separate topics. After 50 years of investigation, it is recognized that there are many similarities as well as differences between the therapeutic principles of treatment of the two diseases.

For operable cases without mediastinal lymph node involvement, surgical resection followed by assessment for adjuvant chemotherapy is recommended. The standard of care for unresectable locally advanced SCLC and NSCLC is early concurrent chemoradiation. For both lung cancer subtypes, cisplatin-etoposide as the chemotherapy component of combined modality therapy has never been demonstrated to be inferior to any other regimen. The median survival for locally advanced disease with initial chemoradiation is approximately the same, with a median survival time of 20 to 24 months and a 5-year survival rate of 20%.

For metastatic disease, the palliative first-line systemic therapy for patients with SCLC and NSCLC without a targetable driver mutation is a platinum-based two-drug chemotherapy combination. For SCLC, platinum and etoposide has generally prevailed as the standard, although platinum plus irinotecan is widely used in Asia. The platinum doublet used for first-line chemotherapy for NSCLC has had a more complex evolution with numerous variations; however, the evidence for improved survival with modern platinum doublets can be questioned even for nonsquamous cancers.[5] In both pathologic types, single agents or dose attenuation with first-line therapy result in inferior outcomes. Three- and four-drug chemotherapy regimens are not better than two-drug regimens. Dose-dense and high-dose cytotoxic regimens do not generate superior survival results. Nonplatinum regimens are not superior to platinum-based two-drug combinations. Four to six cycles of first-line therapy is sufficient for most patients. Maintenance chemotherapy is not recommended for SCLC, whereas it is an option for NSCLC that confers a survival advantage if patients fail to receive second-line therapy.[6]

Second-line treatment for both types of lung cancer is single-agent chemotherapy. Topoisomerase-1 inhibitors have been extensively investigated and used in SCLC. Docetaxel is standard second-line therapy for squamous cancers, whereas docetaxel and pemetrexed have equal efficacy in second-line chemotherapy for nonsquamous cancers.[6] The survival outcome for metastatic SCLC and metastatic NSCLC (without epidermal growth factor receptor gene [*EGFR*] or anaplastic lymphoma receptor tyrosine kinase gene [*ALK*] mutations) is similar, with a median survival time of 11 to 12 months and a 2-year survival rate of 15% to 20%.[5] The discovery of molecular targets in adenocarcinomas that are treatable with approved drugs is a conspicuous difference between

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systemic therapy for NSCLC and that for SCLC. No molecular targets that can be treated with drugs with proven efficacy have as yet been approved for SCLC.[7]

Although the initial response rate to chemotherapy for advanced SCLC of 60% to 70% is approximately double that for NSCLC, the median time for chemotherapy-resistant clones to cause a fatal outcome is approximately the same for both diseases. However, the natural history of metastatic lung cancer unrestrained by any systemic treatment is much worse for SCLC than for NSCLC. The propensity of SCLC for rapid growth and spread is demonstrated in a different way in an article by Silva et al.[8] on outcome of SCLC detected by low-dose computed tomography screening (LDCT) for lung cancer that accompanies this editorial.

In a population of 5134 heavy smokers from Italy, 10 cases of SCLC were reported (eight in the screened group and two in the control group) over 45,141 person-years (22 per 100,000 person-years). The rate of cases of SCLC among all lung cancers diagnosed by screening was 10 in 164 (6%). Cumulative tobacco consumption was 82 pack-years compared with 46 pack-years for NSCLC. The patients with SCLC were somewhat older, with a median age at diagnosis of 65 years compared with 57 years for patients with NSCLC. Six of the eight cases of SCLC in the screened group were asymptomatic. Despite this, most of the neoplasms (seven of 10) had distant spread. Stage Ia disease was found in only one individual; two others had stage III disease. Two patients were treated surgically with lobectomy plus chemotherapy, but both relapsed. Although this is a small data set, poignantly, there were no 3-year survivors.

The large 55,452-patient National Lung Screening Trial showed evidence of a differential benefit by histologic finding of LDCT screening.[9] The 6-year lung cancer survival rate for adenocarcinoma cases specifically was 71.6% for the LDCT screening arm versus 54.5% in the chest radiography screening arm ($p < 0.0001$). Survival rates for all cases of nonsquamous NSCLC were similar to that for adenocarcinoma, with a mortality risk ratio of 0.71, thus demonstrating a substantial benefit of LDCT screening. In contrast, for SCLC, which accounted for 13% of all cancers found in the LDCT arm and 34% of all interval cancers in the study, the 6-year survival in the LDCT arm (n = 143) was 14.4% versus 11.5% in the control arm (n = 163, mortality risk ratio = 0.9; 95% confidence interval: 0.69–1.18). No survival benefit of screening was observed. Cuffe et al.[10] combined the Toronto and Mayo Clinic screening studies and had clinical data on 10 cases of SCLC identified by LDCT screening. One of the six patients with limited-stage disease was suitable for surgical resection, and two patients were disease free at 2 and 9 years. The median survival was 11.3 months. Another 10 cases of SCLC were detected by the Pan-Canadian Lung Cancer Screening Project (Stephen Lam unpublished data). Median smoking exposure was 56 pack-years and 7 of 10 patients were male. Six had limited-stage disease. The two patients (20%) who had peripheral lung tumors suitable for surgical resection are alive 1.2 and 4.8 years after diagnosis. The median survival of this group is 22 months, which is the same as in the report by Silva et al. The slightly longer survival times in these studies are probably related to lead-time bias and small sample size.

The available information supports the widely held belief that LDCT screening is ineffective in reducing mortality due to SCLC. There will be a minority of cases in which a more peripheral SCLC is identified, and if nodal staging is negative, individual lives may be saved by surgical resection and adjuvant chemotherapy. Occasional patients may be cured by the standard combined modality regimen, but that proportion continues to be approximately 20% of patients with limited-stage disease. These are very slim pickings. A more effective screening strategy must await an improvement in technology such as discovery of the elusive biomarker.

Much has changed since Matthews' 1973 lung cancer autopsy paper.[1] Modern preoperative staging paradigms are much more effective in detection of metastases. Although improvement in systemic therapy has been frustratingly slow, combined modality therapy with early concurrent thoracic irradiation and later prophylactic brain irradiation has modestly improved prospects for long-term survival in locally advanced SCLC.[11] The therapeutic principles of systemic treatment of SCLC and NSCLC may be converging again, with immunotherapy becoming the most exciting advance in both histologic types.

Some things have not changed. The virulent natural history of SCLC for rapid growth and spread is as bad as before. Between 60% and 80% of the participants in the Italian, U.S., and Canadian screening studies with SCLC were current smokers. Smoking cessation as part of LDCT screening for lung cancer is essential.

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